



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

CAI *et al.*

Appl. No.: 10/514,427

§ 371 Date: November 16, 2004

For: **Substituted 4-Aryl-4H-pyrrolo[2,3-h]chromenes and Analogs as Activators of Caspases and Inducers of Apoptosis and the Use Thereof**

Confirmation No.: 4080

Art Unit: 1609

Examiner: O'Dell, David K.

Atty. Docket: 1735.0770001/RWE/CJW

**Second Supplemental Information Disclosure Statement  
Filing Under 37 C.F.R. § 1.97(b)**

***Mail Stop Amendment***

Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

Sir:

Listed on accompanying IDS Form, PTO/SB/08B, is information that may be considered material to the examination of this application, in compliance with the duty of disclosure requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98.

The present invention was the result of a collaboration between inventors having an obligation to assign to Cytovia, Inc. (Cytovia) and inventors having an obligation of assignment to Shire Biochem Inc. (Shire). The present application names inventors from Cytovia and Shire and is co-owned by Cytovia and Shire.

At a time prior to the priority date for the present application, a conference call was conducted between the Cytovia and Shire inventors. In advance of this conference call, a document was prepared by Dr. Sui Xiong Cai of Cytovia which depicted 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-4H-pyrrolo[2,3-h]chromene, a compound recited in Example 16 and claim 23 of the present application. During the conference call, it was agreed that this compound would be made at Cytovia. It was also

agreed that 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-8-oxo-4,8-dihydro-oxazo[4,5-*h*]chromene would be made at Shire<sup>1</sup>.

2-Amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene was then made and tested in an *in vitro* assay by Cytovia inventors and found to be highly active in inhibiting proliferation of two breast tumor cell lines.

A face-to-face meeting was held at a later time between the Cytovia and Shire inventors. In advance of this conference call, a document was prepared by Dr. Cai which summarized the testing data for 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene and proposed additional targets for synthesis, including:

2-amino-4-(5-chloropyridin-3-yl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(5-nitropyridin-3-yl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(5-cyanopyridin-3-yl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(3-bromo-4-hydroxy-5-methoxyphenyl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(3,5-dimethoxyphenyl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

4-(3-bromo-4-hydroxy-5-methoxyphenyl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(5-methylpyridin-3-yl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

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<sup>1</sup> 2-Amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-8-oxo-4,8-dihydro-oxazo[4,5-*h*]chromene is recited in claims 5 and 20 of U.S. Pat. 6,858,607 owned by Cytovia.

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-ethyl-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-cyclopropyl-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-(2-dimethylaminoethyl)-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-(2-diethylaminoethyl)-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-4*H*-imidazo[4,5-*h*]chromene,

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-8-oxo-4,8-dihydro-oxazo[4,5-*h*]chromene, and

4-(3-bromo-4-(sodium phosphate)-5-methoxyphenyl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene.

Also in advance of the face-to-face meeting, a document was prepared by Giorgio Attardo of Shire which listed the following targets for synthesis:

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-4*H*-imidazo[4,5-*h*]chromene,

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-8-oxo-4,8-dihydro-oxazo[4,5-*h*]chromene,

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-7-methyl-4*H*-imidazo[4,5-*h*]chromene,

4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

4-(3-bromo-4,5-dimethoxyphenyl)-7-methyl-4*H*-pyrrolo[2,3-*h*]chromene,

4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-8-oxo-4,8-dihydro-oxazo[4,5-*h*]chromene,

4-(3-bromo-4,5-dimethoxyphenyl)-7-methyl-8-oxo-4,8-dihydro-oxazo[4,5-*h*]chromene,

4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-7-methyl-4,8-dihydro-oxazo[4,5-*h*]chromene.

The two documents were discussed at the face-to-face meeting.

After the face-to-face meeting, a document was prepared by Giorgio Attardo which confirmed the targets discussed in the meeting and assigned targets to Cytovia and Shire for synthesis.

After the face-to-face meeting, additional compounds were prepared and provisional application 60/378,079 was filed May 16, 2002, the priority application for the above-captioned application.

Applicants also wish to bring to the attention of the Examiner that copending Application 11/150,586, filed June 13, 2005 (and claiming priority to U.S. Appln. 60/163,584, filed November 5, 1999) is assigned to Cytovia while the present application is assigned to Cytovia and Shire.

Applicants also wish to bring to the attention of the Examiner that copending Application 11/072,499, filed March 7, 2005 (and claiming priority to U.S. Appln.

60/163,548, filed November 5, 1999) is assigned to Cytovia while the present application is assigned to Cytovia and Shire.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

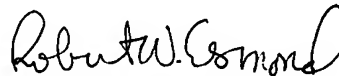
This Information Disclosure Statement is being filed prior to the issuance of the first Office Action on the merits. No statement or fee is required.

It is respectfully requested that the Examiner indicate in the official file wrapper of this patent application that the documents have been considered.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

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